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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/786,988	01/23/1997	DANIEL P. LITTLE	U/18485-0012	5922

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EXAMINER

BEX, PATRICIA K

ART UNIT PAPER NUMBER

1743

43

DATE MAILED: 03/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

AS-43

Office Action Summary	Application No. 08/786,988	Applicant(s) LITTLE ET AL.	
	Examiner P. Kathryn Bex	Art Unit 1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 November 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,9-34,40-51,54-61 and 63-94 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

- 5) ☐ Claim(s) _____ is/are allowed.

- 6) ☒ Claim(s) 1-6,9-34,40-51,54-61 and 63-94 is/are rejected.

- 7) ☐ Claim(s) _____ is/are objected to.

- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>41</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

1. The cancellation of claim 62 is acknowledged and has been entered into the record.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-6, 9-34, 40-51 and 54-61, 63-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for capillaries capable of dispensing within the range of 0.2-2 nL, does not reasonably provide enablement for the vesicle to dispense in the "sub to low" range. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. The specification does not support the broad limitation of "sub to low" range, but rather sites a specific range i.e. 0.2-2 nL. Therefore, the specification does not enable one of ordinary skill to make/use the invention commensurate in the scope with these claims.

Claims 1-6, 9-34, 40-51 and 54-61, 63-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Independent claims 1, 5, 25, 31, 40, 63, 63, 66 and 70 now recite the limitation "such that spot-to-spot characteristics are reproducible in the array". No such recitation was found in the specification. Moreover, it is not clear from the claim how moving the vesicle adjacent the surface of the substrate will produce

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“defined and controlled” volumes of fluid such that “spot-to-spot characteristics are reproducible in the array”.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 13, recites the vesicle to eject from the chamber a "sub to low" nanoliter volume. The terms "sub" and "low" are relative terms which render the claim indefinite. The terms "sub" and "low" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to what Applicant considers a "sub" or "low" amount of nanoliter volume.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-6, 9-34, 40-51, 54-61, 63-69 and 87-93 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang *et al* (“Micro-preparation Procedure for High-sensitivity Matrix-assisted Laser Desorption Ionization Mass Spectrometry”, JMS Letters).

Zhang *et al* teach a method and an apparatus for dispensing a target material on a

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multi-well sample holder (Fig. 1, page 1769, line 6-8). The method comprises the steps of providing a packed capillary (e.g. vesicle) having an interior chamber containing a fluid, disposing the vesicle adjacent a first location on the surface of a holder to spot an area on the holder less than 0.3 mm^2 , controlling the vesicle to eject from the chamber 5 nanoLiter volume, (page 1769, 2nd full paragraph) of the fluid to dispense the fluid at the first location of the surface of the multi-well sample holder. Next, moving the vesicle to a set of positions so that fluid is dispensed from the vesicle at each location of the set for forming an array of fluid material (Fig. 1) which clearly shows the array wherein the spot-to-stop characteristics are reproducible (page 1769, 2nd column, 1st full paragraph). Additionally, Zhange *et al* do specifically recite the step of performing MALDI mass spectrometry analysis for the material for measuring the molecular masses of the biological molecules.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 70-86 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ershow *et al.* (USP 5,756,050) in view of Jespersen *et al.* (Attomole detection of Proteins by Matrix-assisted Laser Desorption/Ionization Mass Spectrometry with the Use of Picoliter Vials) or Li *et al.* (Analysis of Single Mammalian Cell Lysates by Mass Spectrometry).

Ershow *et al.* disclose an apparatus and method for dispensing 0.3 nanoliter, (column 3, lines 1-4) of a material on the surface of a substrate 16 substantially as claimed. The method comprises the steps of providing a pin assembly 1 having a plurality of elongated vesicles 2 arranged as an array for dispensing a liquid therefrom (Figs. 1-2), wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoLiter volume for fluid; loading a volume of fluid from a fluid source 14 onto the end of the vesicles; disposing the pin assembly to align the vesicles at a first set of locations adjacent to the surface of the substrate 16; and contacting the loading fluid to the surface of the substrate is formed (Figs. 3-4). Ershow *et al.* fail to specifically recite a diagnostic tool comprising a mass spectrometer. However, the use of such a spectrometer for identifying polymers is considered conventional in the art, see Jespersen *et al.* or Li *et al.*

Jespersen *et al.* teaches an apparatus and method for the detection of biomolecules by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Jespersen *et al.* recognizes the significant improvement in the absolute detection limits attainable by the reduction of the sample volume from a few microliters down to 250 picoliters. Jespersen *et al.* teach use of an array picoliter vials etched onto a silicon wafer. This silicon wafer is glued onto a MALDI stainless-steel target for detection by the mass spectrometer. The picoliter vials were

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filled manually under an optical microscope using laboratory-made glass micropipettes, resulting in pipettes with an outer tip diameter smaller than 100 micrometers.

Similarly, Li *et al* teach a MALDI mass spectrometry in combination with a capillary loaded with sample to deposit sample on a probe surface. Using capillaries with internal diameters from 10-200 micrometer, the volume delivered can be varied over a wide range (i.e. 20 picoliter to 100 nanoliters). The capillaries dispensing the sample spots onto the matrix layer for analysis by a high-resolution TOF-MS.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method and apparatus of applying nanoliter volumes as taught by Ershow *et al* with detection system, as taught by Jespersen *et al* or Li *et al*, in order to provide a significant reduction of both the sample volume needed and three orders of magnitude improvement in detection limits (see third full paragraph of Jespersen *et al*).

Response to Arguments

11. Applicant's arguments with respect to claims 1-6, 9-34, 40-51 and 54-61, 63-94 have been considered but have not been found persuasive. With respect to the rejection of claims 70-86 and 94 under 35 U.S.C. 103(a) as being unpatentable over Ershow *et al* (USP 5,756,050) in view of Jespersen *et al* (Attomole detection of Proteins by Matrix-assisted Laser Desorption/Ionization Mass Spectrometry with the Use of Picoliter Vials) or Li *et al* (Analysis of Single Mammalian Cell Lysates by Mass Spectrometry), Applicant argues Ershow *et al* is directed to solving problems associated with evaporation and viscosity and does not teach or suggest the volumes dispensed must be controlled and defined to produce a substrate with uniform spots. Examiner does not agree since Ershow *et al* clearly discusses microdispensing of

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a plurality of 0.3 nanoliter of a material on the surface of a substrate 16 (column 3, lines 1-4).

The substrate having areas 17 of gel being regularly spaced (e.g. array) so as to follow the layout of the rods (column 5, lines 50-55). Additionally, Ershow *et al* discuss the invention able to deliver a volume from 0.3 to 50 nl with a high degree of accuracy and reproducibility (column 3, lines 2-13, column 6, lines 9-15).

Conclusion

12. No claims allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Kathryn Bex whose telephone number is (703) 306-5697. The examiner can normally be reached on Mondays-Thursdays, alternate Fridays from 6:00 am to

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3:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 308-4037.

The fax number for the organization where this application or proceeding is assigned is (703) 872-9310 for official papers prior to mailing of a Final Office Action. For after-Final Office Actions use (703) 872-9311. For unofficial or draft papers use fax number (703) 305-7719. Please label all faxes as official or unofficial. The above fax numbers will allow the paper to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0661.

Kathryn Bex

P. Kathryn Bex
Patent Examiner
AU 1743
March 14, 2003

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